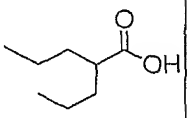
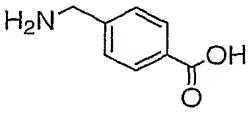
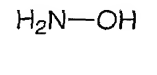
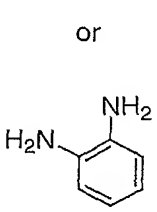
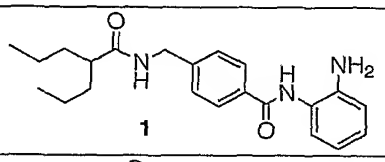
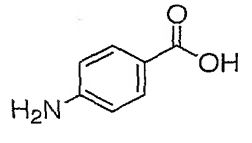
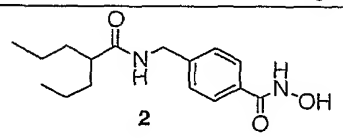
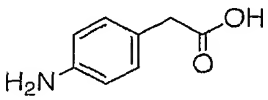
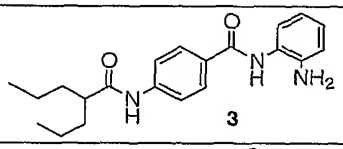
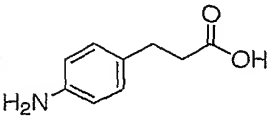
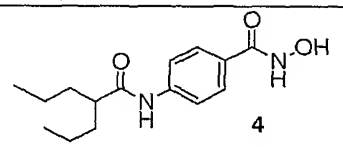
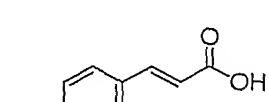
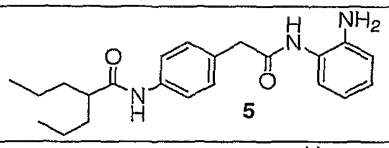
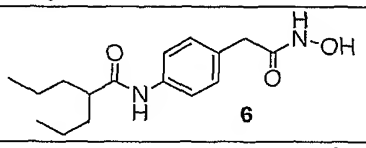
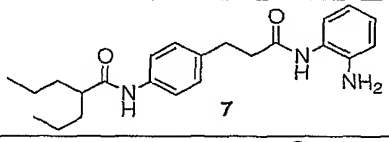
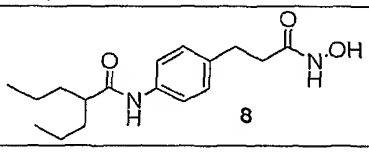
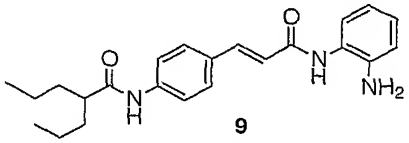
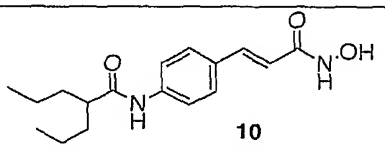
Valproic acid	Linker	Zn^2 -chelating group	Derivatives
		 	 1
			 2
			 3
			 4
			 5
			 6
			 7
			 8
			 9
			 10

FIGURE 1

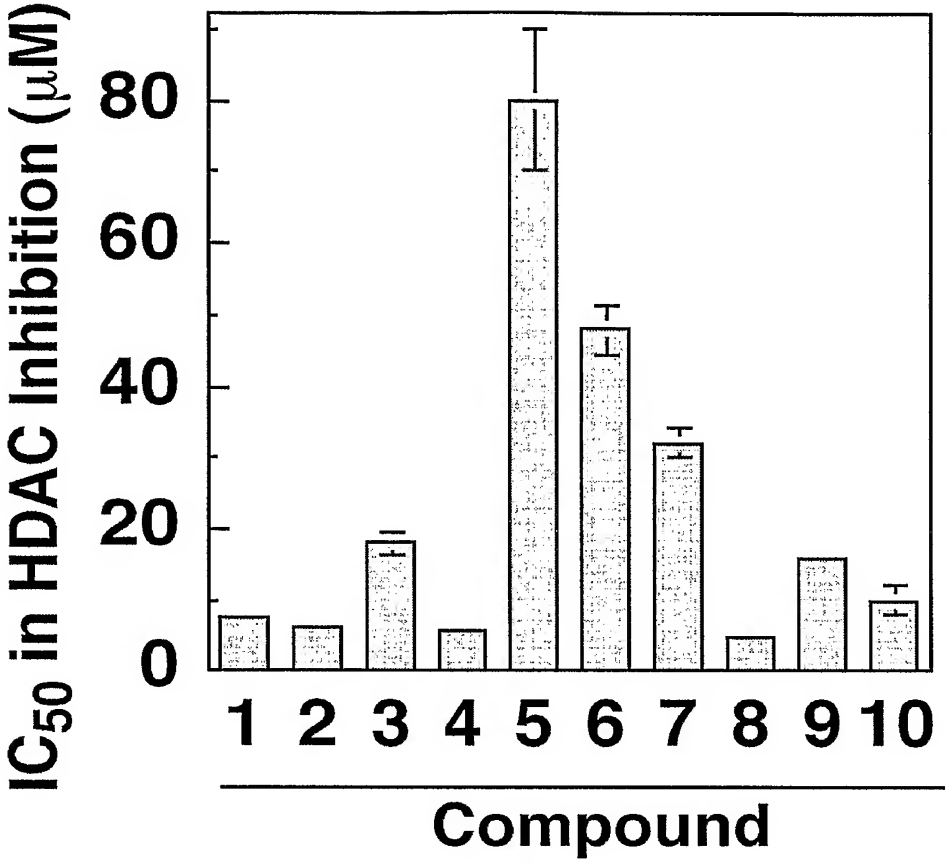

IC50 in HDAC Inhibition (μM)
0
20
40
60
80
1 2 3 4 5 6 7 8 9 10
Compound

FIGURE 2

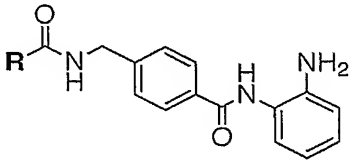
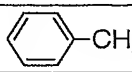
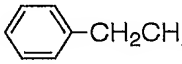
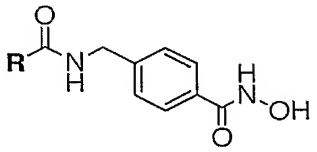
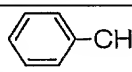
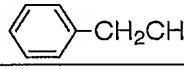
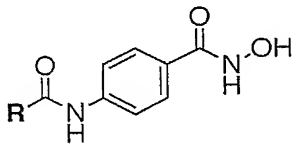
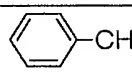
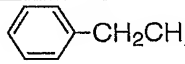
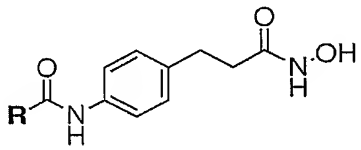
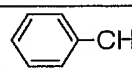
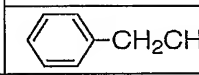
	R	Compounds	IC_{50} (μM)
	$CH_3CH_2CH_2$-	**11**	6.0 ± 0.5
		**12**	5.2 ± 0.4
		**13**	4.3 ± 0.3
	$CH_3CH_2CH_2$-	**14**	3.6 ± 0.5
		**15**	2.5 ± 0.3
		**16**	1.2 ± 0.1
	$CH_3CH_2CH_2$-	**17**	1.5 ± 0.2
		**18**	0.11 ± 0.01
		**19 (HTPB)**	0.044 ± 0.006
	$CH_3CH_2CH_2$-	**20**	1.6 ± 0.2
		**21**	0.67 ± 0.08
		**22**	0.53 ± 0.06

FIGURE 3

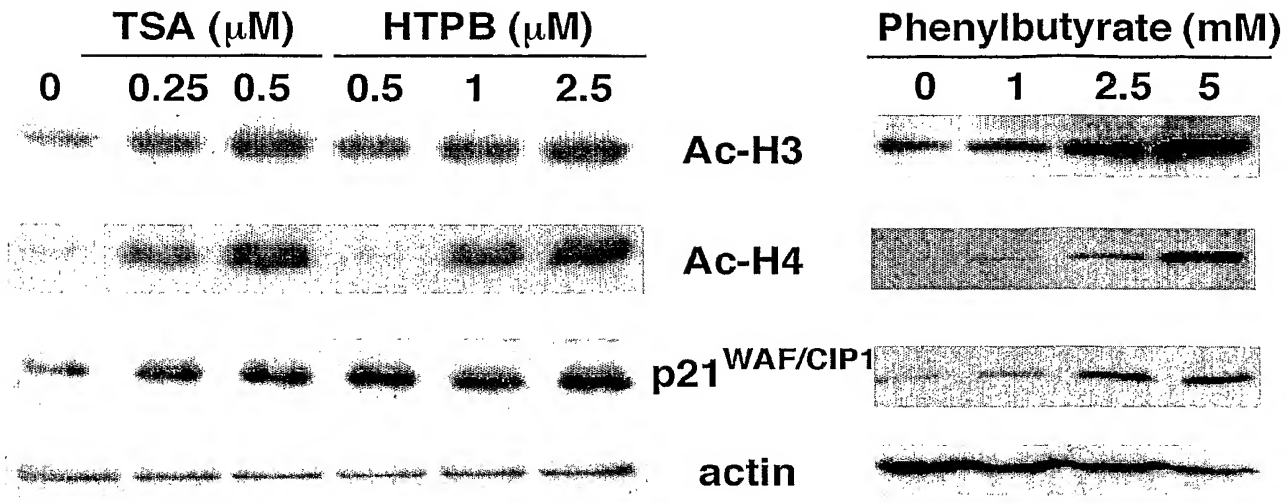

TSA (μM)
HTPB (μM)
Phenylbutyrate (mM)
0
0.25
0.5
0.5
1
2.5
0
1
2.5
5
Ac-H3
Ac-H4
p21WAF/CIP1
actin

FIGURE 4

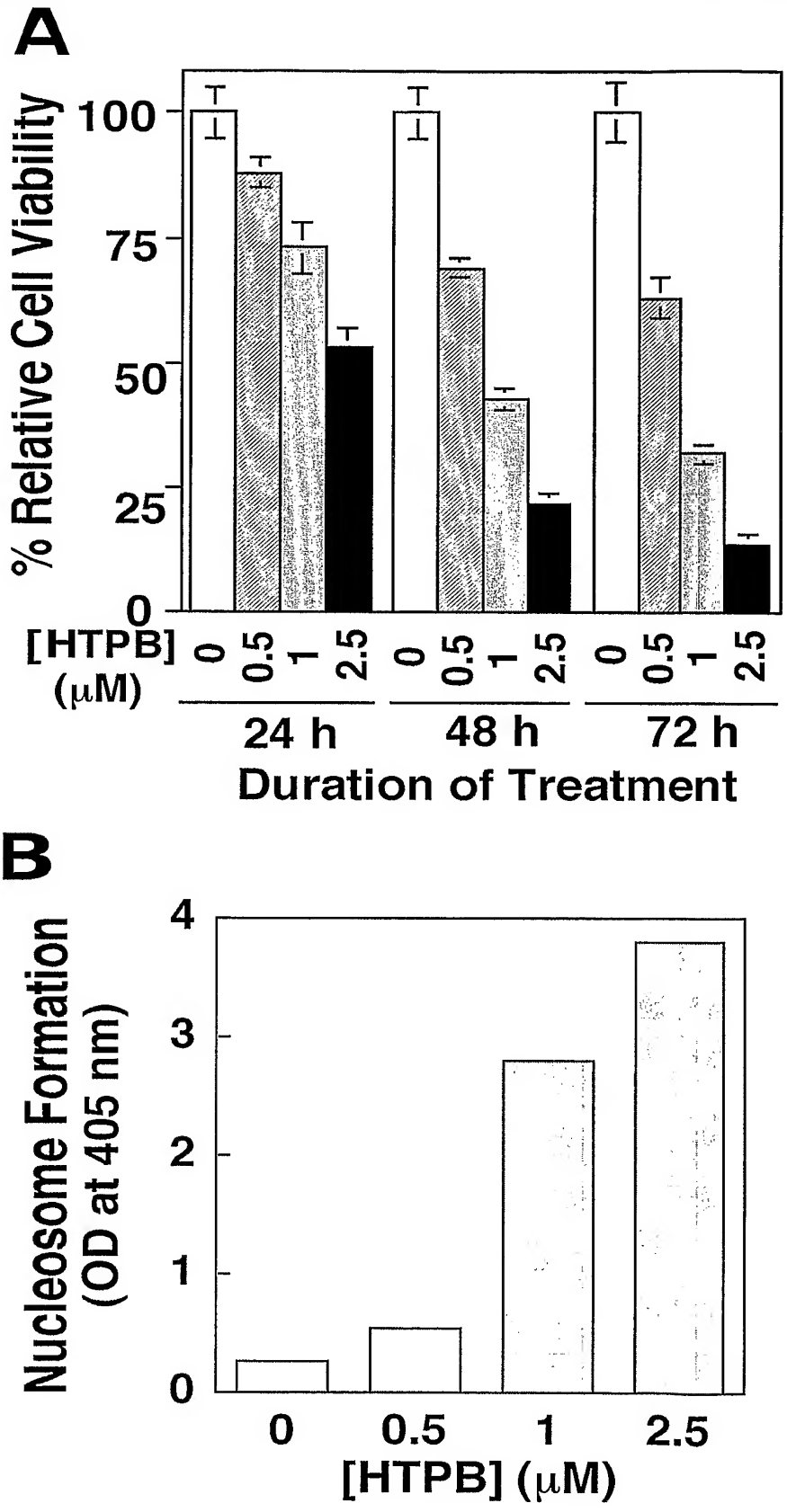
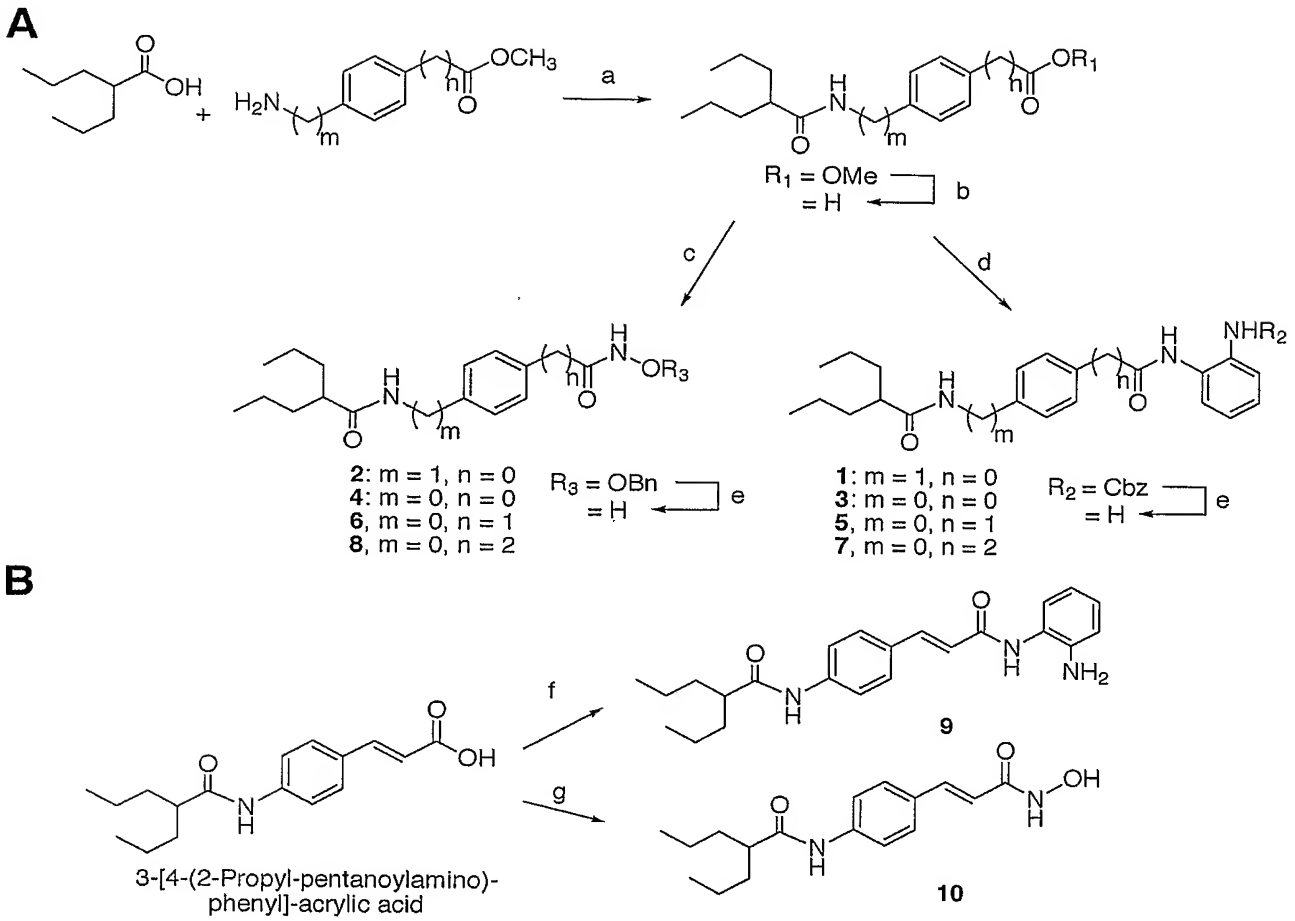

A
% Relative Cell Viability
100
75
50
25
0
[HTPB] (μM)
0
0.5
1
2.5
24 h
48 h
72 h
Duration of Treatment
B
Nucleosome Formation (OD at 405 nm)
4
3
2
1
0
0
0.5
1
2.5
[HTPB] (μM)

FIGURE 5

Scheme 1[a]



[a]Reagents: (a) EDC, THF; (b) KOH/MeOH, 80 °C; (c) $NH_2OBn \cdot HCl$, BOPCl, Et_3N; (d) (2-aminopheny)carbamic acid benzyl ester, EDC, THF; (e) 10% Pd/C, H_2, MeOH/THF; (f) $NH_2OH \cdot HCl$, EDC, HOBT, Et_3N; (g) *o*-phenylene diamine, EDC, THF.

FIGURE 6

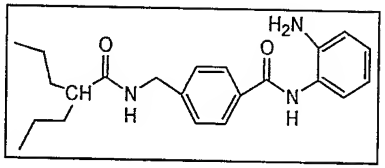
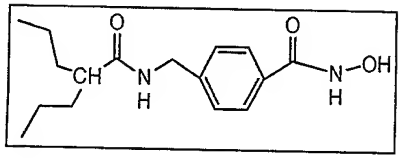
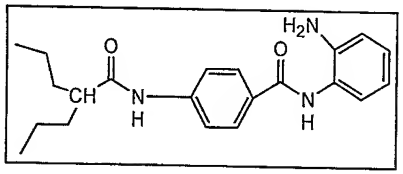
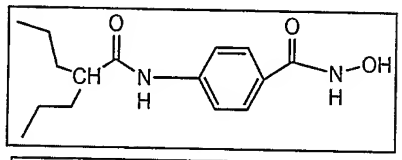
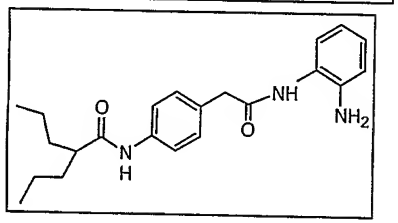
Compound	Structure	HDAC IC50 (uM)	Cell Viability(DU145, 10%FBS,3d)(uM)	Nomenclature
1		8		N-(2-Amino-phenyl)-4-[(2-propyl-pentanoylamino)-methy1]-benzamide
2		5		N-Hydroxy-4-[(2-propyl-pentanoylamino)-methy1]-benzamide
3		20		N-(2-Amino-phenyl)-4-(2-propyl-pentanoylamino)-benzamide
4		4		N-Hydroxy-4-(2-propyl-pentanoylamino)-benzamide
5		80		2-Propyl-pentanoic acid {4-[2-amino-phenylcarbamoyl)-methyl]-phenyl}-amide

FIGURE 7 (Frame 1)

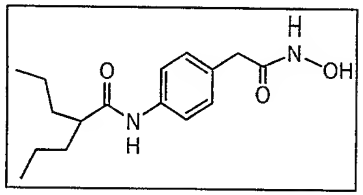
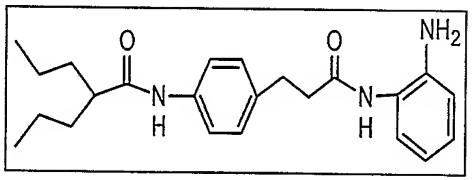
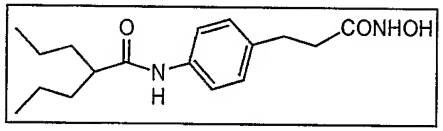
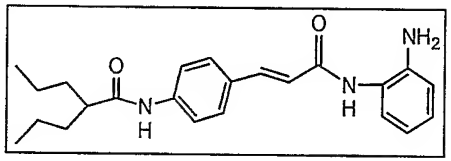
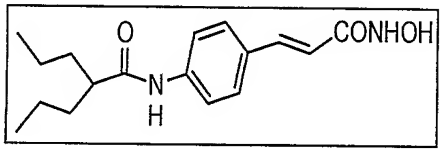
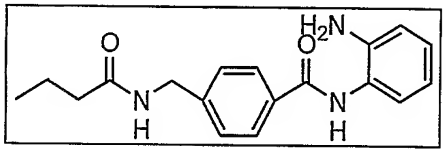
6		50	2-Propyl-pentanoic acid (4-hydroxycarbamoyl-methyl-phenyl)-amide
7		35	2-Propyl-pentanoic acid {4-[2-amino-phenylcarbamoyl)-ethyl]-phenyl}-amide
8		3	2-Propyl-pentanoic acid [4-(2-hydroxycarbamoyl-ethyl)-phenyl]-amide
9		15	2-Propyl-pentanoic acid {4-2-(2-amino-phenylcarbamoyl)-vinyl]-phenyl}-amide
10		10	2-Propyl-pentanoic acid [4-(2-hydroxycarbamoyl-vinyl)-phenyl]-amide
11		6	N-(2-Amino-phenyl)-4-(butyrylamino-methyl)-benzamide

FIGURE 7 (Frame 2)

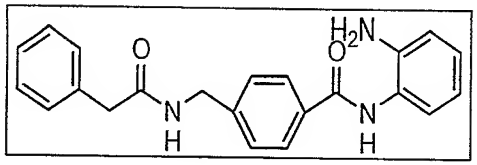
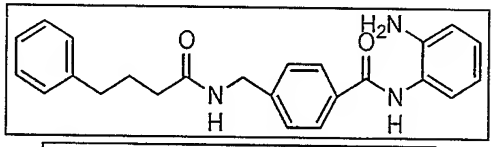
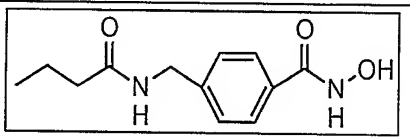
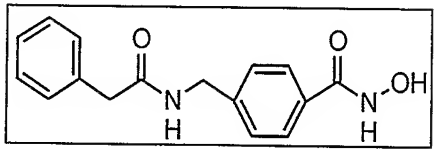
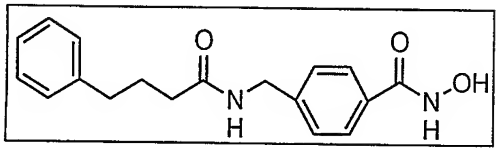
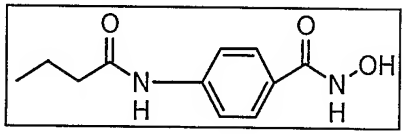
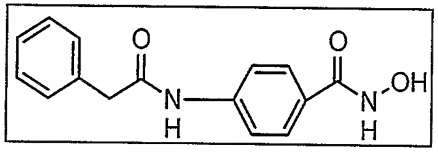
12		5.2		N-(2-Amino-phenyl)-4-(phenylacetylamino-methyl)-benzamide
13		4.3		N-(2-Amino-phenyl)-4-[(4-phenyl-butyrylamino-methyl]-benzamide
14		3.6		4-(Butyrylamino-methyl)-*N*-hydroxy-benzamide
15		2.5		*N*-hydroxy-4-(phenylacetylamino-methyl)-benzamide
16		1.2		*N*-hydroxy-4-[(4-phenyl-butyrylamino)-methyl]-benzamide
17		1.5	15	4-Butyrylamino-*N*-hydroxy-benzamide
18		0.11	1.5	N-hydroxy-4-phenylacetylamino-benzamide

FIGURE 7 (Frame 3)

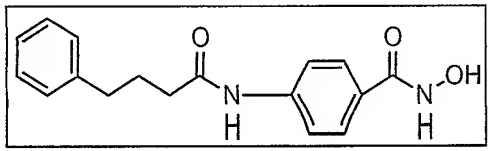
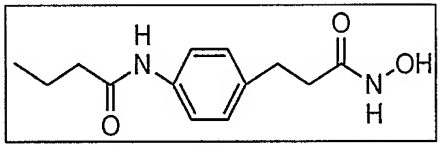
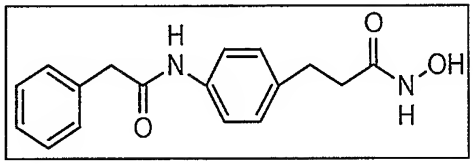
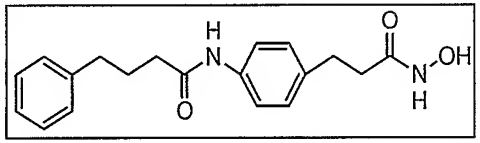
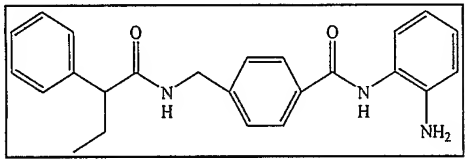
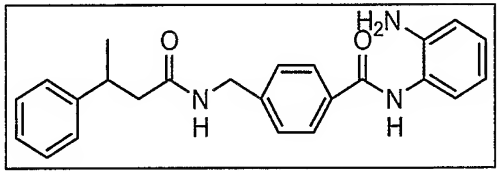
19		0.05	0.8	N-hydroxy-4-(4-phenylbutyrylamino)-benzamide
20		1.6		*N*-[4-(2-Hydroxycarbamoyl-ethyl)-phenyl]-butyramide
21		0.67		*N*-hydroxy-3-(4-phenylacetylamino-phenyl)-propionamide
22		0.53		*N*-[4-(2-Hydroxycarbamoyl-ethyl)-phenyl]-4-phenyl-butyramide
23		8		N-(2-Amino-phenyl)-4-[(2-phenyl-butyrylamino-methyl]-benzamide
24		6		N-(2-Amino-phenyl)-4-[(3-phenyl-butyrylamino-methyl]-benzamide

FIGURE 7 (Frame 4)

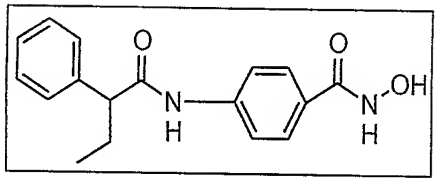
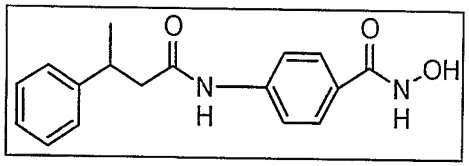
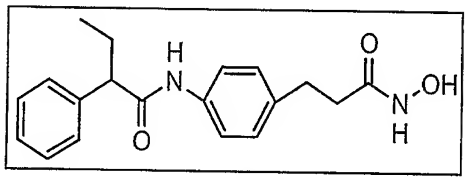
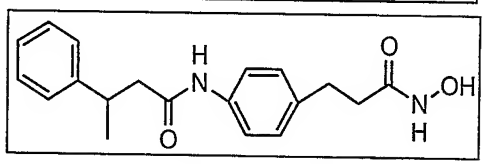
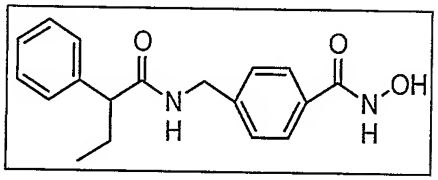
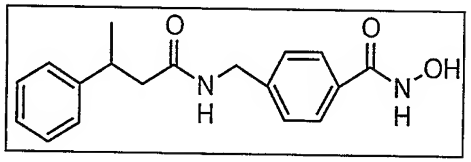
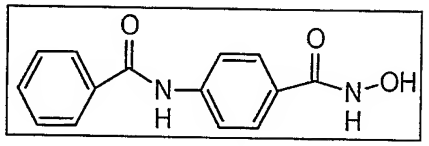
25		0.04	N-hydroxy-4-(2-phenylbutyrylamino)-benzamide
26		0.09	N-hydroxy-4-(3-phenylbutyrylamino)-benzamide
27		0.45	*N*-[4-(2-Hydroxycarbamoyl-ethyl)-phenyl]-2-phenyl-butyramide
28		0.6	*N*-[4-(2-Hydroxycarbamoyl-ethyl)-phenyl]-3-phenyl-butyramide
29		2.3	*N*-hydroxy-4-[(2-phenyl-butyrylamino)-methyl]-benzamide
30		1.5	*N*-hydroxy-4-[(3-phenyl-butyrylamino)-methyl]-benzamide
31			4-Benzoylamino-*N*-hydroxy-benzamide

FIGURE 7 (Frame 5)

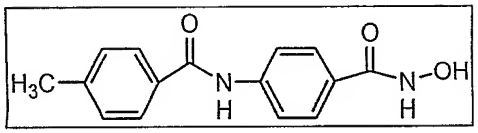
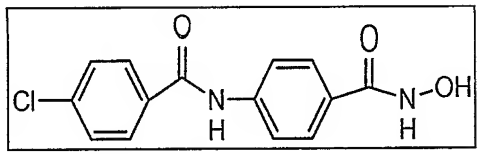
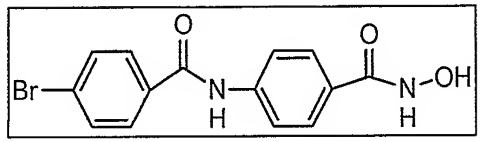
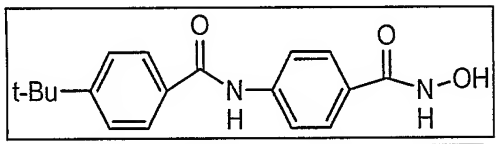
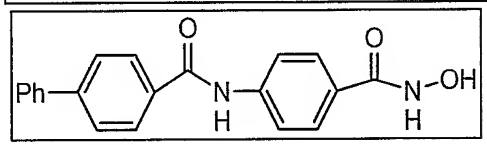
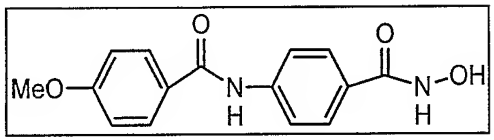
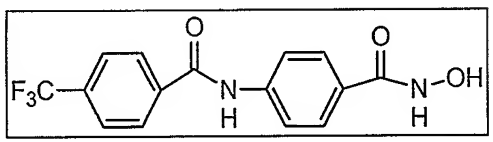
32			4-(4-methyl)-Benzoylamino-*N*-hydroxy-benzamide
33			4-(4-chloro)-Benzoylamino-*N*-hydroxy-benzamide
34			4-(4-bromo)-Benzoylamino-*N*-hydroxy-benzamide
35			4-(4-*tert*-butyl)-Benzoylamino-*N*-hydroxy-benzamide
36			4-(4-phenyl)-Benzoylamino-*N*-hydroxy-benzamide
37			4-(4-methoxyl)-Benzoylamino-*N*-hydroxy-benzamide
38		1.3	4-(4-trifluoromethyl)-Benzoylamino-*N*-hydroxy-benzamide

FIGURE 7 (Frame 6)

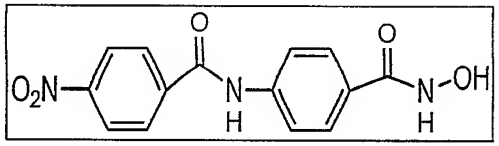
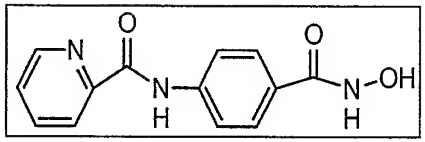
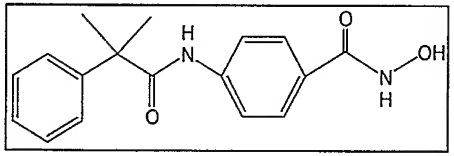
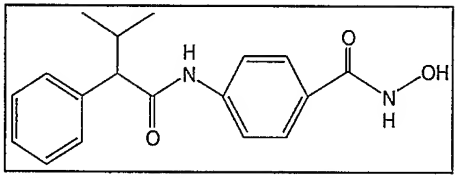
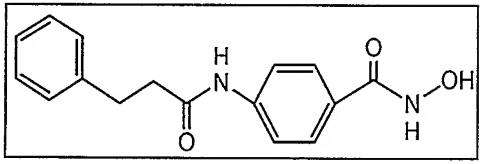
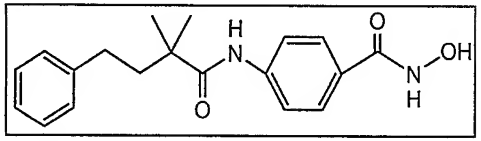
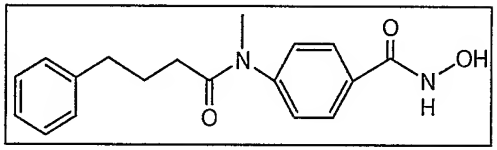
39				4-(4-nitro)-Benzoylamino-*N*-hydroxy-benzamide
40				Pyridine-2-carboxylic acid (4-hydroxycarbamoyl-phenyl)-amide
41		0.1	1.5	*N*-hydroxy-4-(2-methyl-2-phenyl-propionylamino)-benzamide
42		0.06	0.4	*N*-hydroxy-4-(3-methyl-2-phenyl-butyrylamino)-benzamide
43			1.5	*N*-hydroxy-4-(3-phenyl-propionylamino)-benzamide
44		0.025	0.4	4-(2,2-Dimethyl-4-phenyl-butyrylamino)-N-hydroxy-benzamide
45		0.5		*N*-hydroxy-4-[methyl-(4-phenyl-butyryl)-amino]-benzamide

FIGURE 7 (Frame 7)

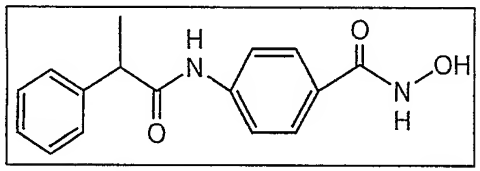
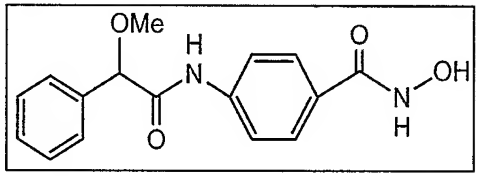
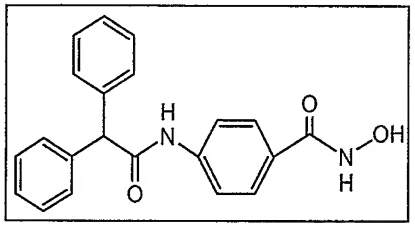
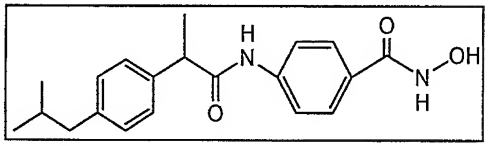
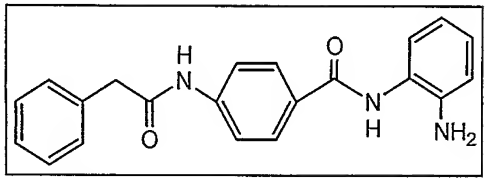
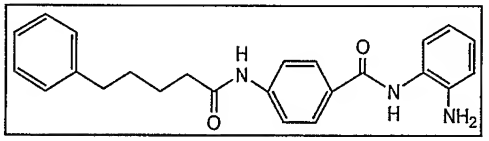
46				*N*-hydroxy-4-(2-phenyl-propionylamino)-benzamide
47				*N*-hydroxy-4-(2-methoxy-2-phenyl-acetylamino)-benzamide
48				4-Diphenylacetylamino-*N*-hydroxy-benzamide
49				*N*-hydroxy-4-[2-(4-isobutyl-phenyl)-propionylamino]-benzamide
50		1.2		*N*-(2-Amino-phenyl)-4-phenylacetylamino-benzamide
51		1.3	1.3	*N*-(2-Amino-phenyl)-4-(5-phenyl-pentanoylamino)-benzamide

FIGURE 7 (Frame 8)

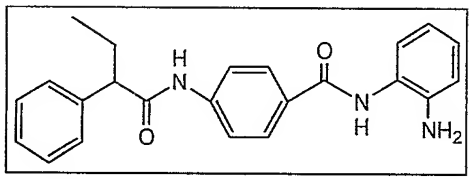
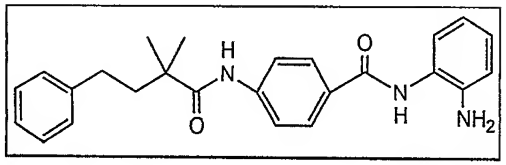
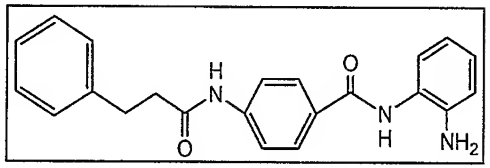
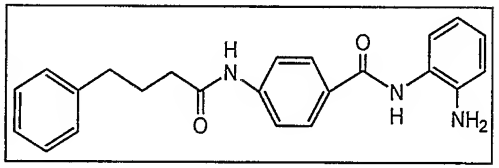
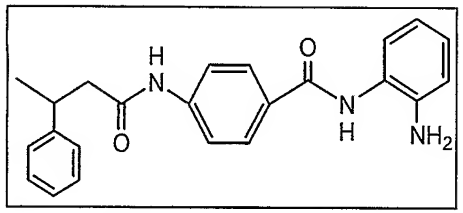
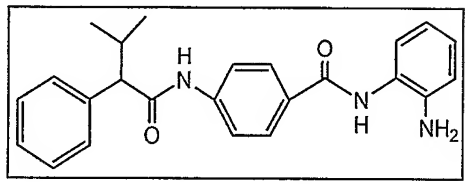
52		1	0.7	*N*-(2-Amino-phenyl)-4-(2-phenyl-butyrylamino)-benzamide
53		0.4	0.8	*N*-(2-Amino-phenyl)-4-(2,2-dimethyl-4-phenyl-butyrylamino)-benzamide
54				*N*-(2-Amino-phenyl)-4-(3-phenyl-propionylamino)-benzamide
55				*N*-(2-Amino-phenyl)-4-(4-phenyl-butyrylamino)-benzamide
56				*N*-(2-Amino-phenyl)-4-(3-phenyl-butyrylamino)-benzamide
57				*N*-(2-Amino-phenyl)-4-(3-methyl-2-phenyl-butyrylamino)-benzamide

FIGURE 7 (Frame 9)

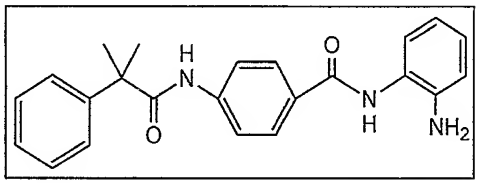
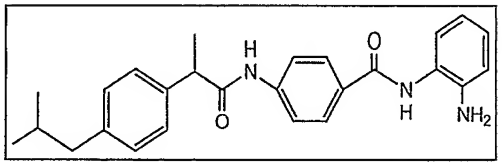
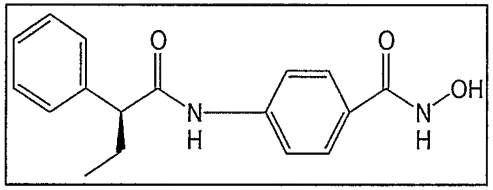
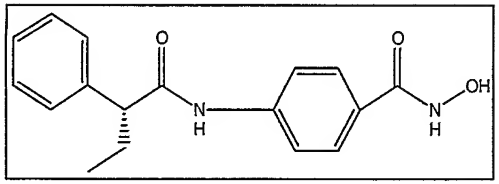
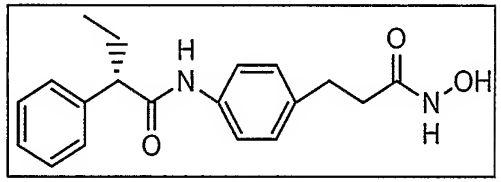
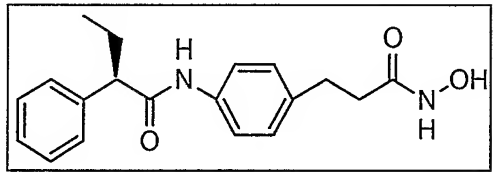
58				*N*-(2-Amino-phenyl)-4-(2-methyl-2-phenyl-propionylamino)-benzamide
59				*N*-(2-Amino-phenyl)-4-[2-(4-isobutyl-phenyl)-propionylamino]-benzamide
60		0.034	0.6	N-hydroxy-4-[2-(S)-phenylbutyrylamino]-benzamide
61		0.068	0.5	N-hydroxy-4-[2-(R)-phenylbutyrylamino]-benzamide
62		0.08		*N*-[4-(2-Hydroxycarbamoyl-ethyl)-phenyl]-2-(S)-phenyl-butyramide
63		0.06		*N*-[4-(2-Hydroxycarbamoyl-ethyl)-phenyl]-2-(R)-phenyl-butyramide

FIGURE 7 (Frame 10)

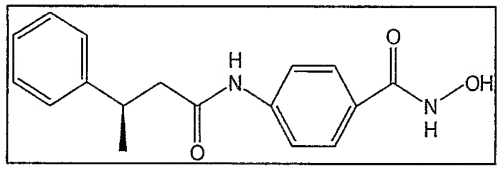
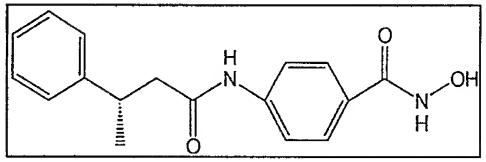
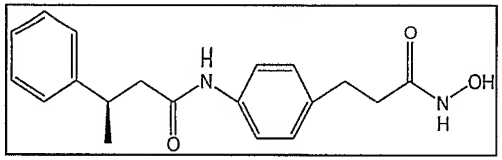
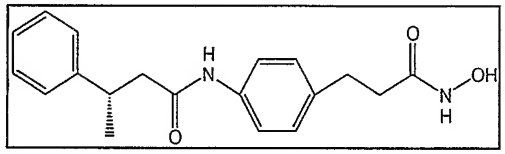
64		N-hydroxy-4-(3-(S)-phenylbutyrylamino)-benzamide
65		N-hydroxy-4-(3-(R)-phenylbutyrylamino)-benzamide
66		N-hydroxy-4-[3-(S)-phenylbutyrylamino]-benzamide
67		N-hydroxy-4-[3-(R)-phenylbutyrylamino]-benzamide

FIGURE 7 (Frame 11)

Zinc-chelating motifs:

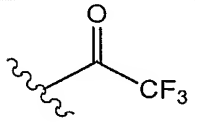
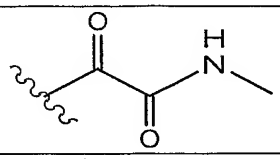
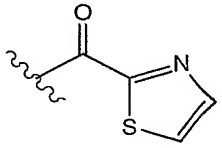
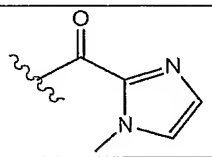
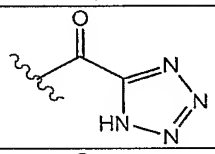
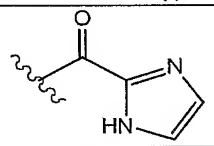
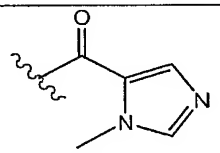
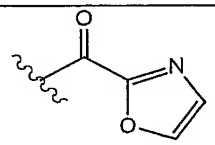
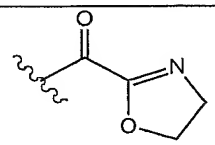
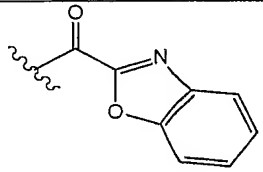
Structure	Name
	Trifluoromethyl ketone
	α-keto Amide
	α-keto Thiazole
	2-keto 1-Methyl-1*H*-imidazole
	α-keto 1*H*-Tetrazole
	α-keto 1*H*-Imidazole
	5-keto 1-Methyl-1*H*-imidazole
	α-keto Oxazole
	α-keto 4,5-Dihydro-oxazole
	α-keto Bezooxazole

FIGURE 8 (Frame 1)

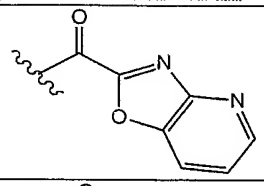
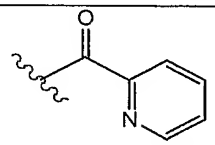
	α-keto Oxazolo[4,5-*b*]pyridine
	α-keto Pyridine

FIGURE 8 (Frame 2)

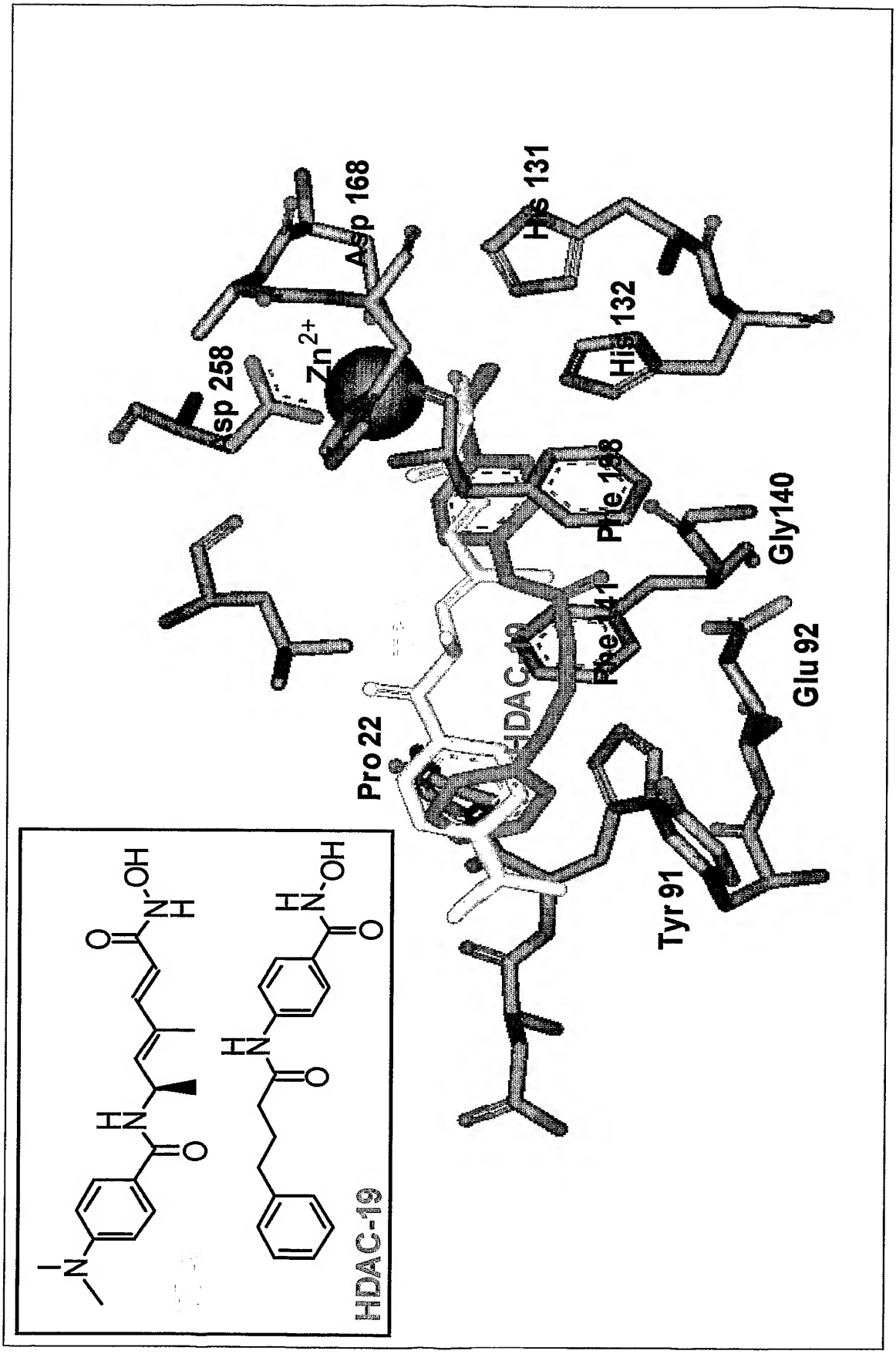

HDAC-19
Pro 22
HDAC-2
Phe 141
Phe 198
Gly140
Glu 92
Tyr 91
Asp 258
Zn2+
Asp 168
His 131
His 132

FIGURE 9

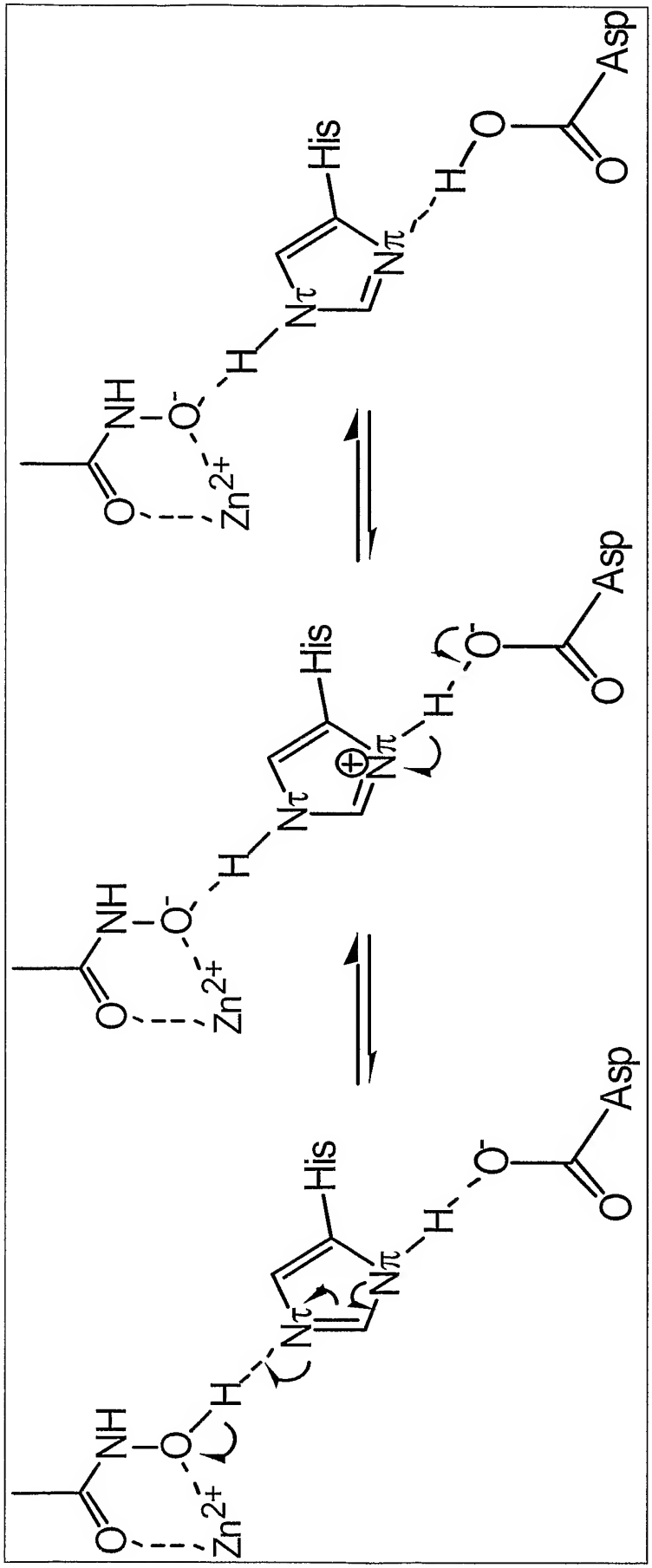


FIGURE 10

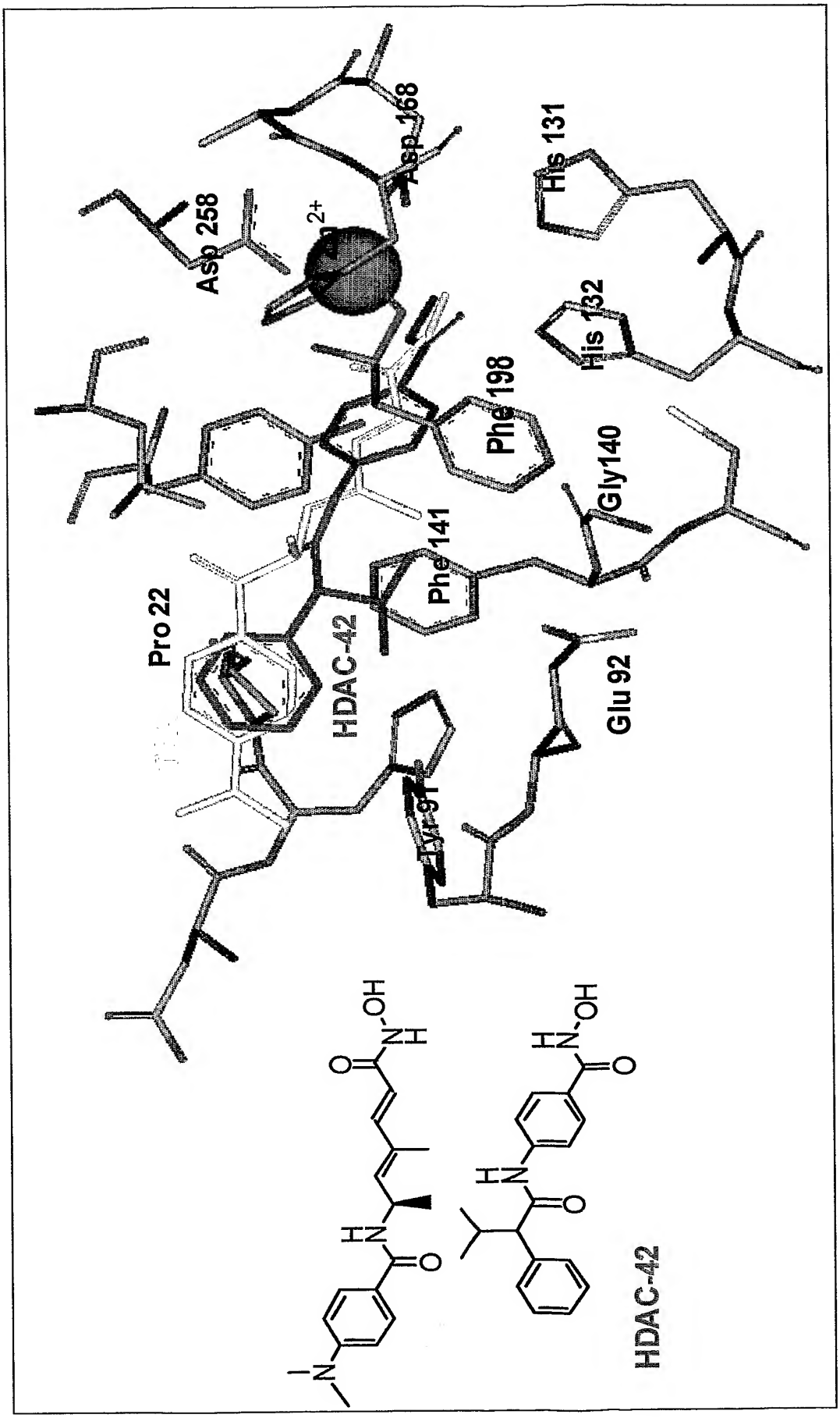

Asp 168
Asp 258
2+
His 131
His 132
Phe 198
Gly140
Phe 141
Pro 22
HDAC-42
Glu 92
Tyr 91
HDAC-42

FIGURE 11

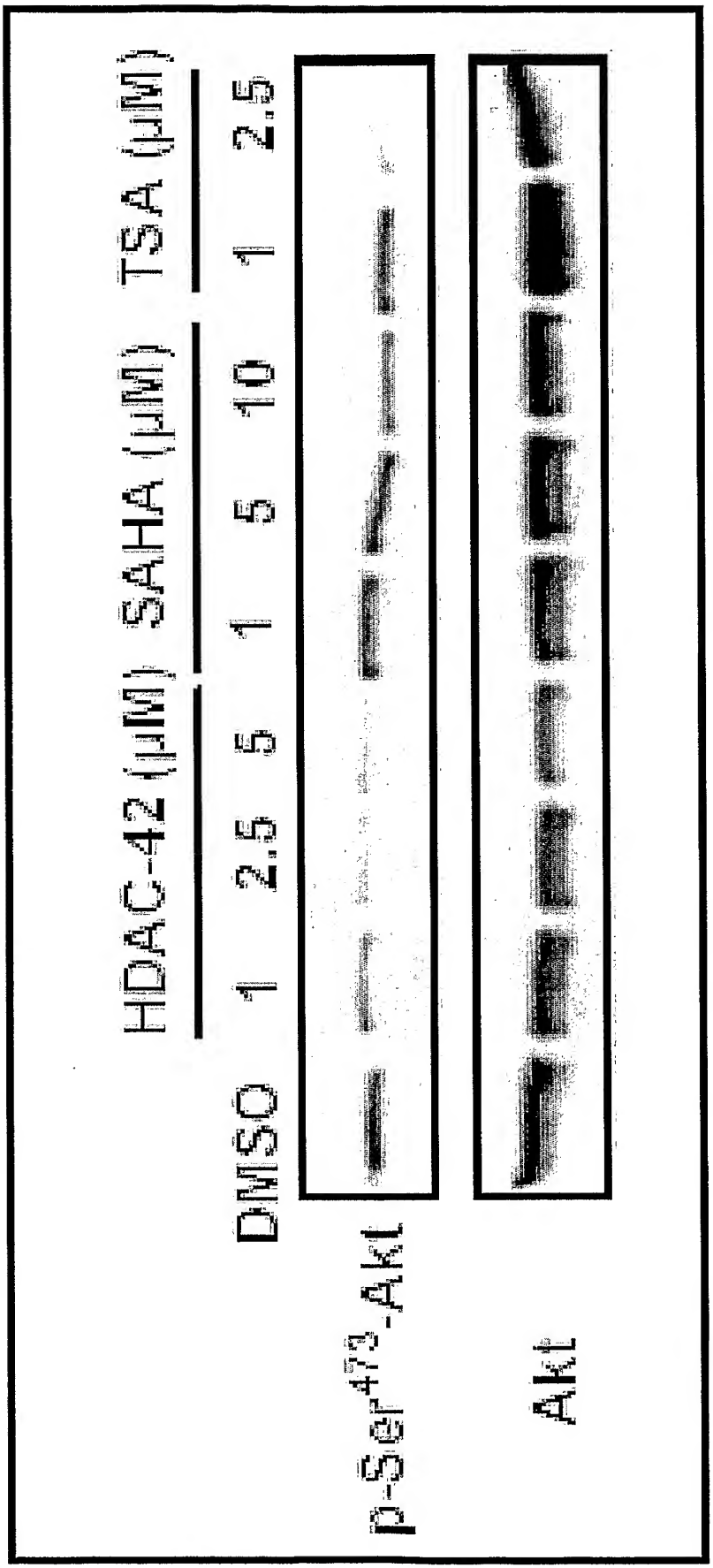


FIGURE 12

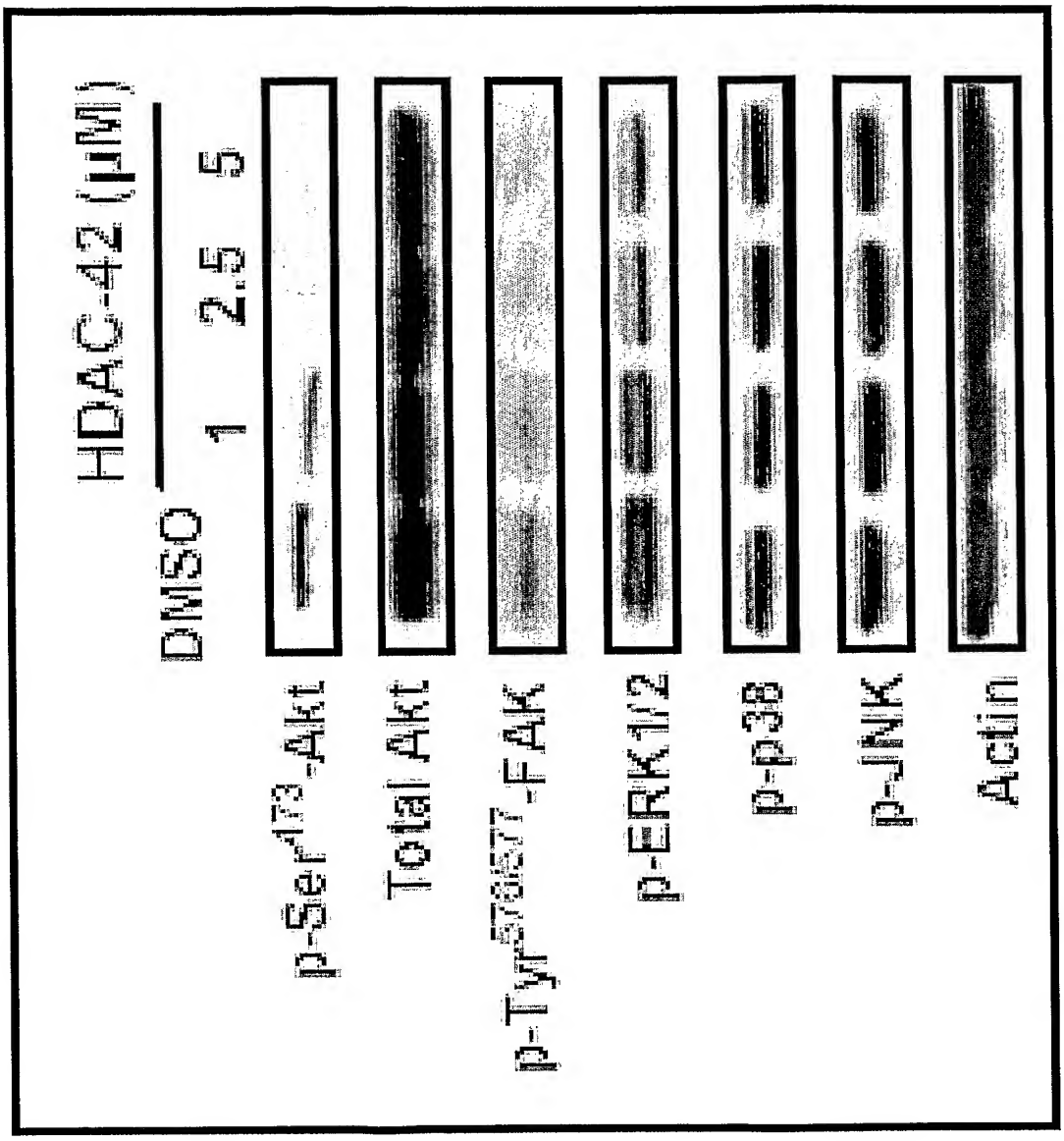

HDAC-42 (μM)
DMSO 1 2.5 5
p-Ser473-Akt
Total Akt
p-Tyr861-FAK
p-ERK1/2
p-p38
p-JNK
Actin

FIGURE 13

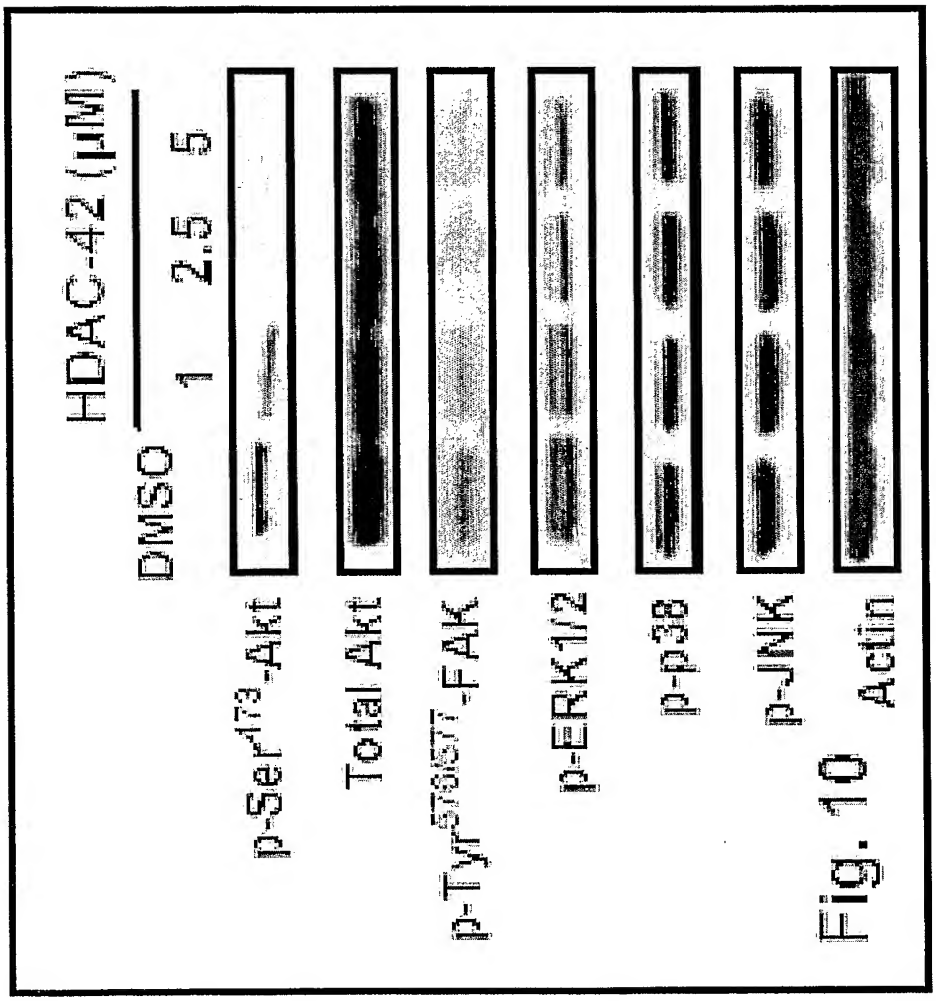

HDAC-42 (μM)
DMSO
1
2.5
5
p-Ser473-Akt
Total Akt
p-Tyr576/577-FAK
p-ERK1/2
p-p38
p-JNK
Actin
Fig. 10

FIGURE 14

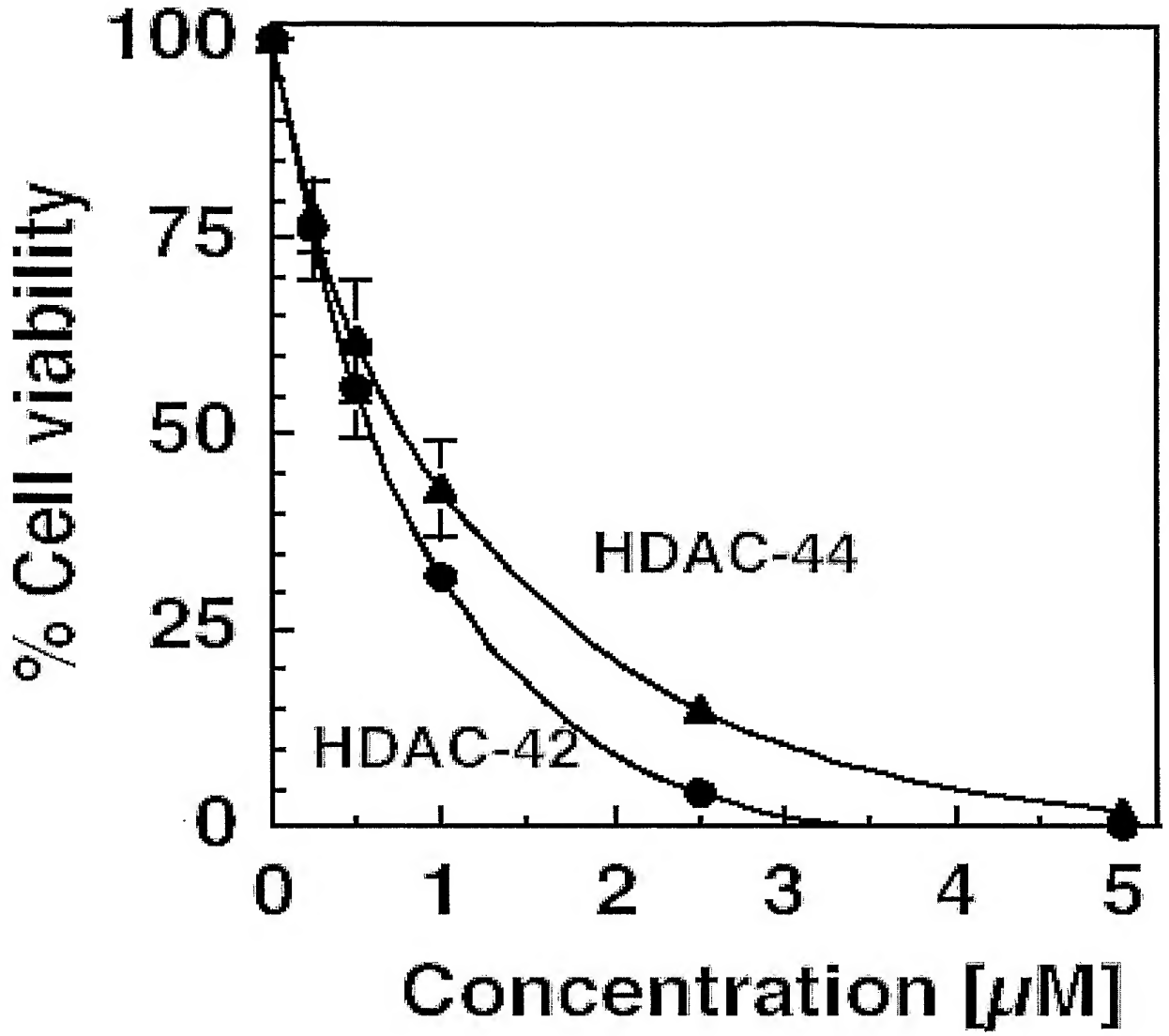

100
75
50
25
0
% Cell viability
HDAC-44
HDAC-42
0
1
2
3
4
5
Concentration [μM]

FIGURE 15

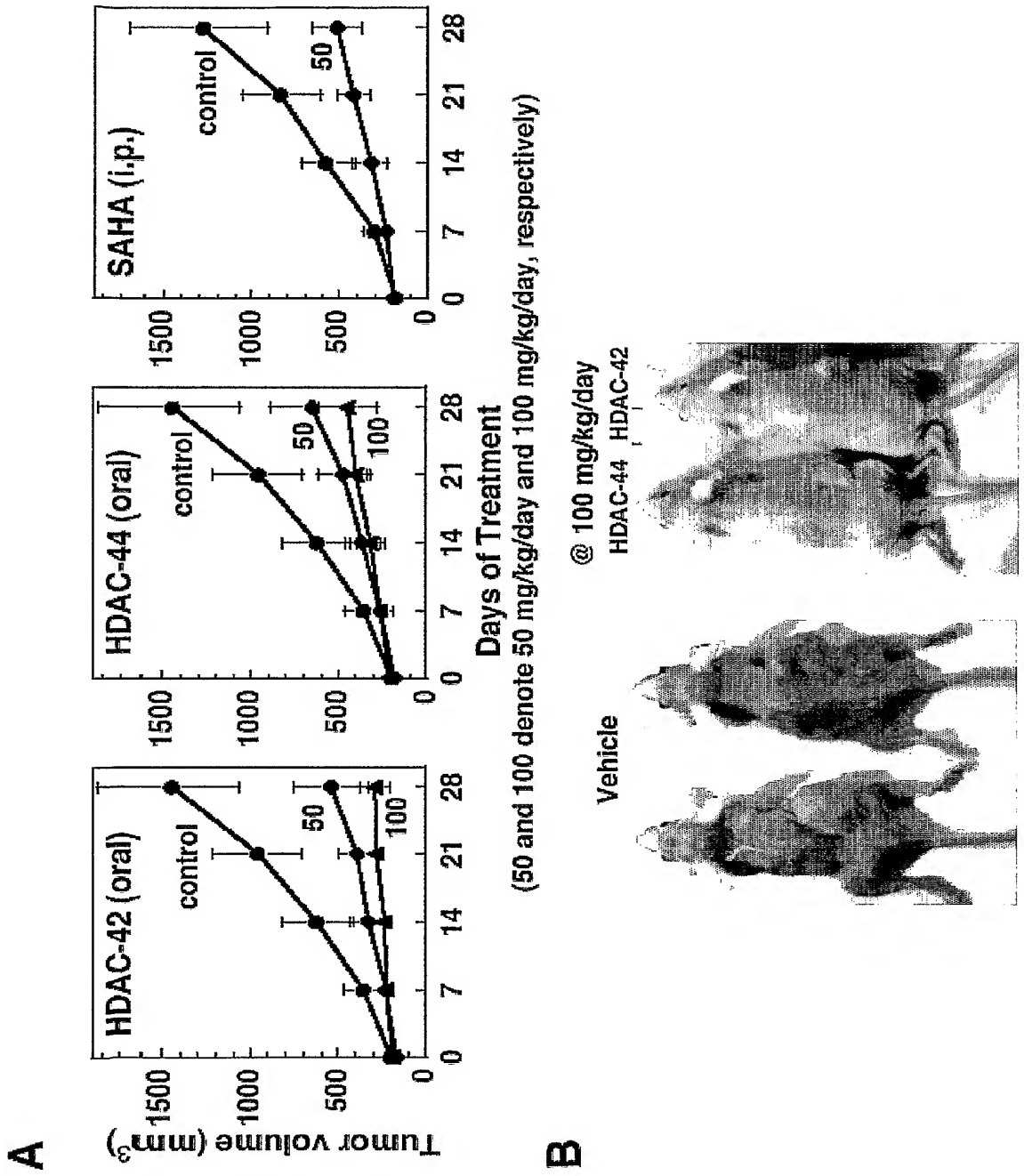

A
Tumor volume (mm³)
HDAC-42 (oral)
HDAC-44 (oral)
SAHA (i.p.)
control
50
100
0
500
1000
1500
0
7
14
21
28
Days of Treatment
(50 and 100 denote 50 mg/kg/day and 100 mg/kg/day, respectively)
B
Vehicle
@ 100 mg/kg/day
HDAC-44
HDAC-42

FIGURE 16

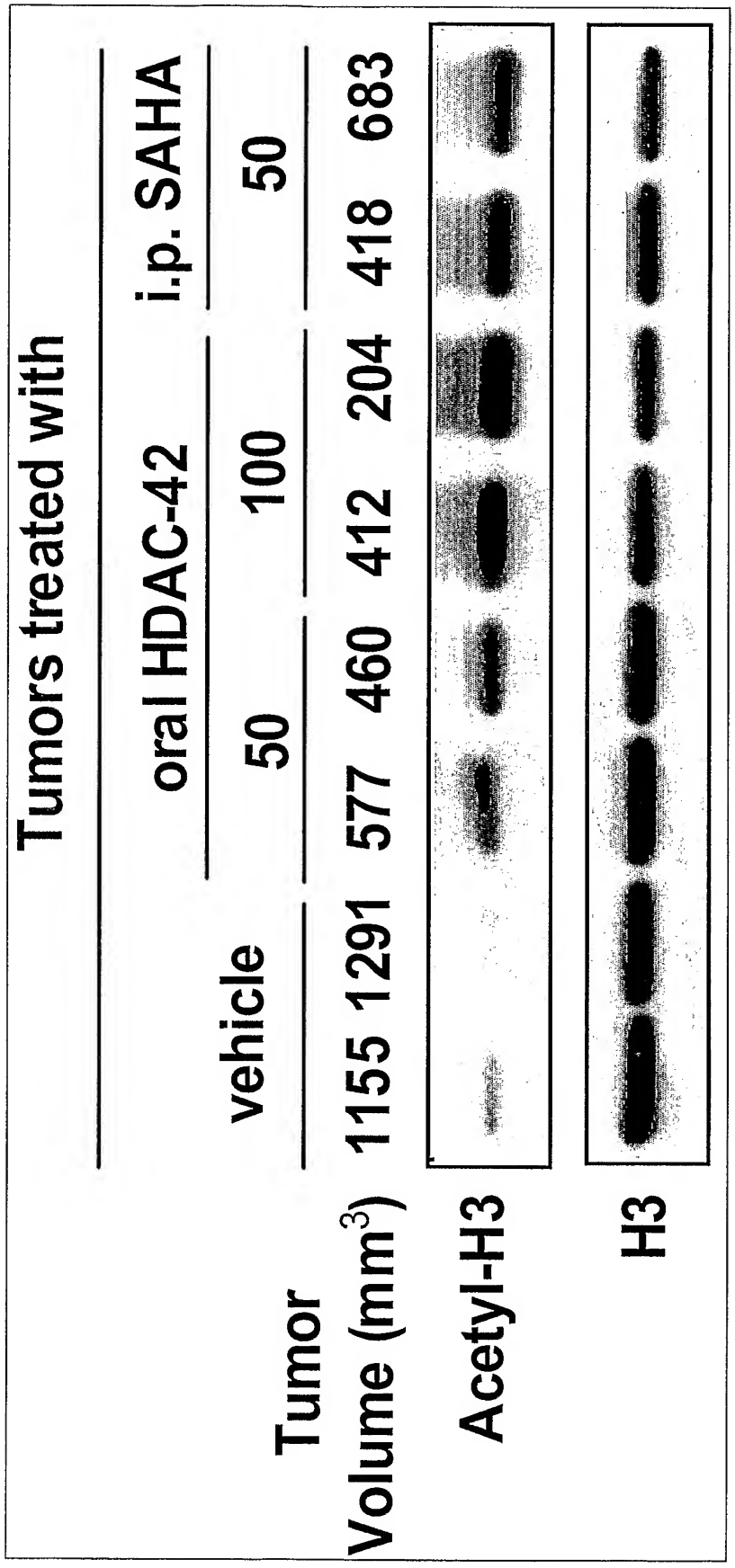

Tumors treated with
oral HDAC-42
i.p. SAHA
vehicle
50
100
50
Tumor Volume (mm3)
1155 1291
577
460
412
204
418
683
Acetyl-H3
H3

FIGURE 17

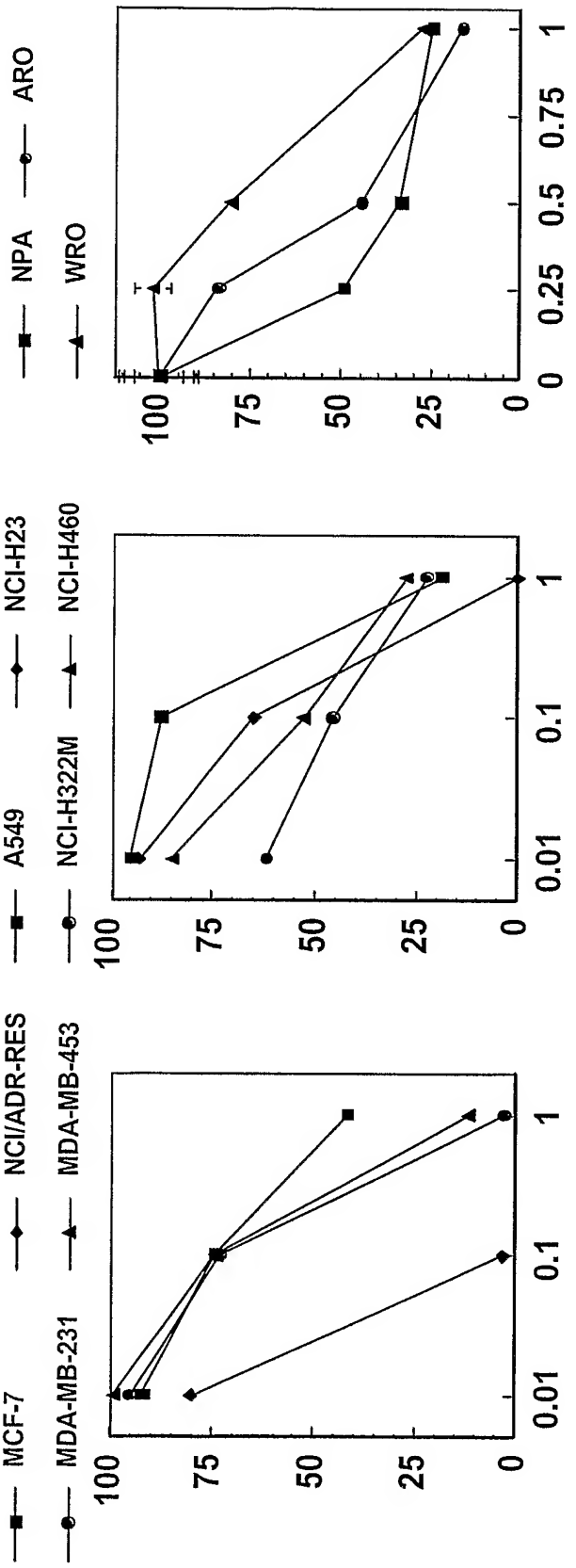

MCF-7
NCI/ADR-RES
MDA-MB-231
MDA-MB-453
A549
NCI-H23
NCI-H322M
NCI-H460
NPA
ARO
WRO
100
75
50
25
0
0.01
0.1
1
0.25
0.5
0.75

FIGURE 18

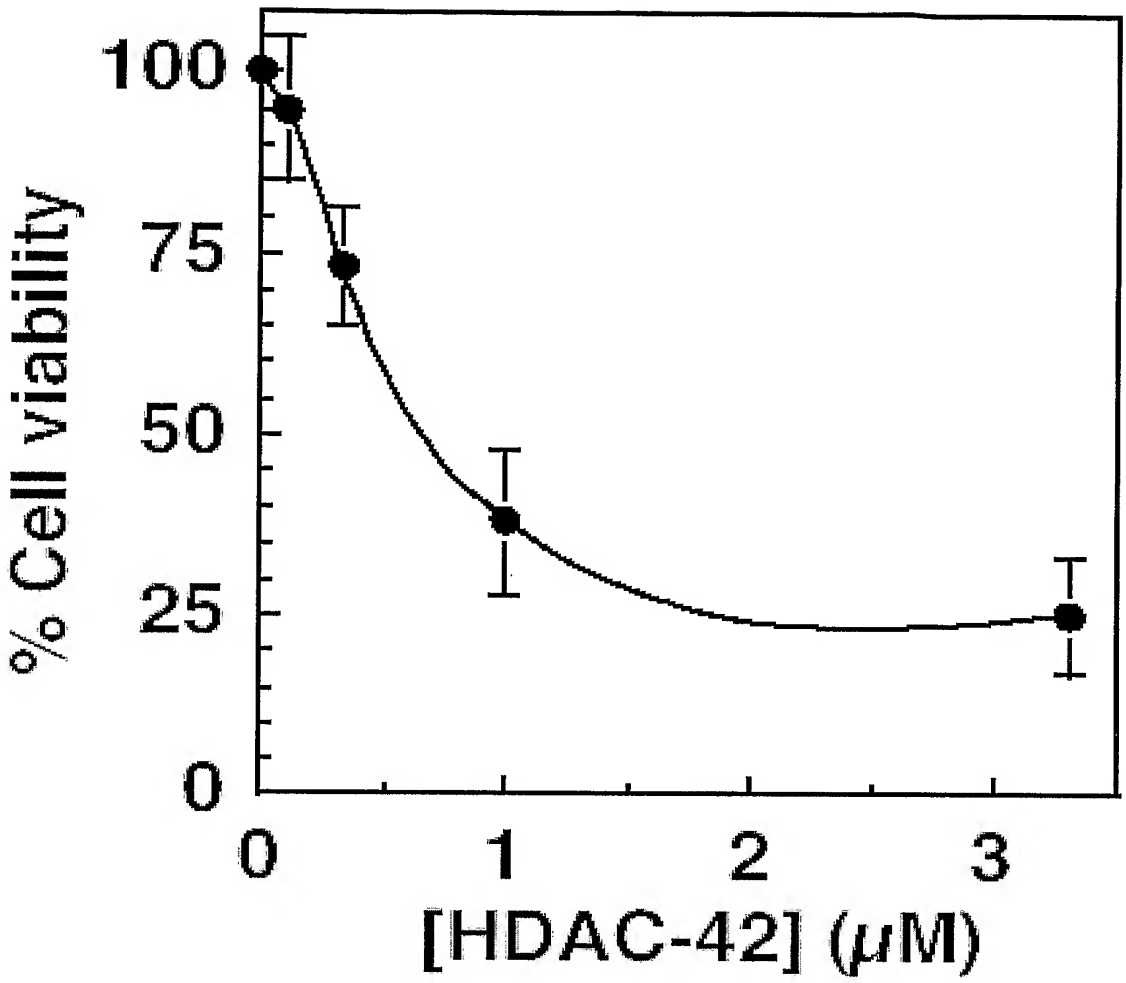


FIGURE 19

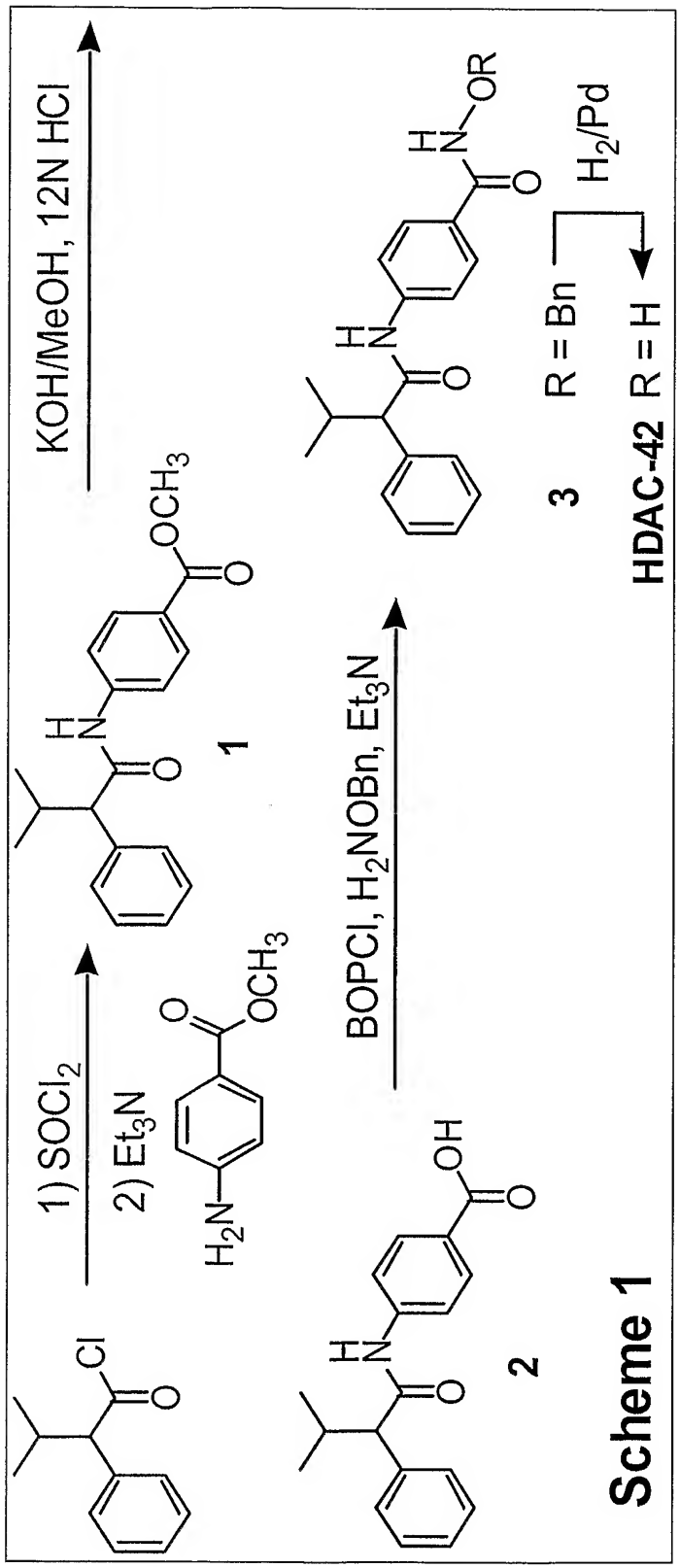

1) SOCl2
2) Et3N
KOH/MeOH, 12N HCl
BOPCl, H2NOBn, Et3N
H2/Pd
R = Bn
R = H
1
2
3
HDAC-42
Scheme 1

FIGURE 20

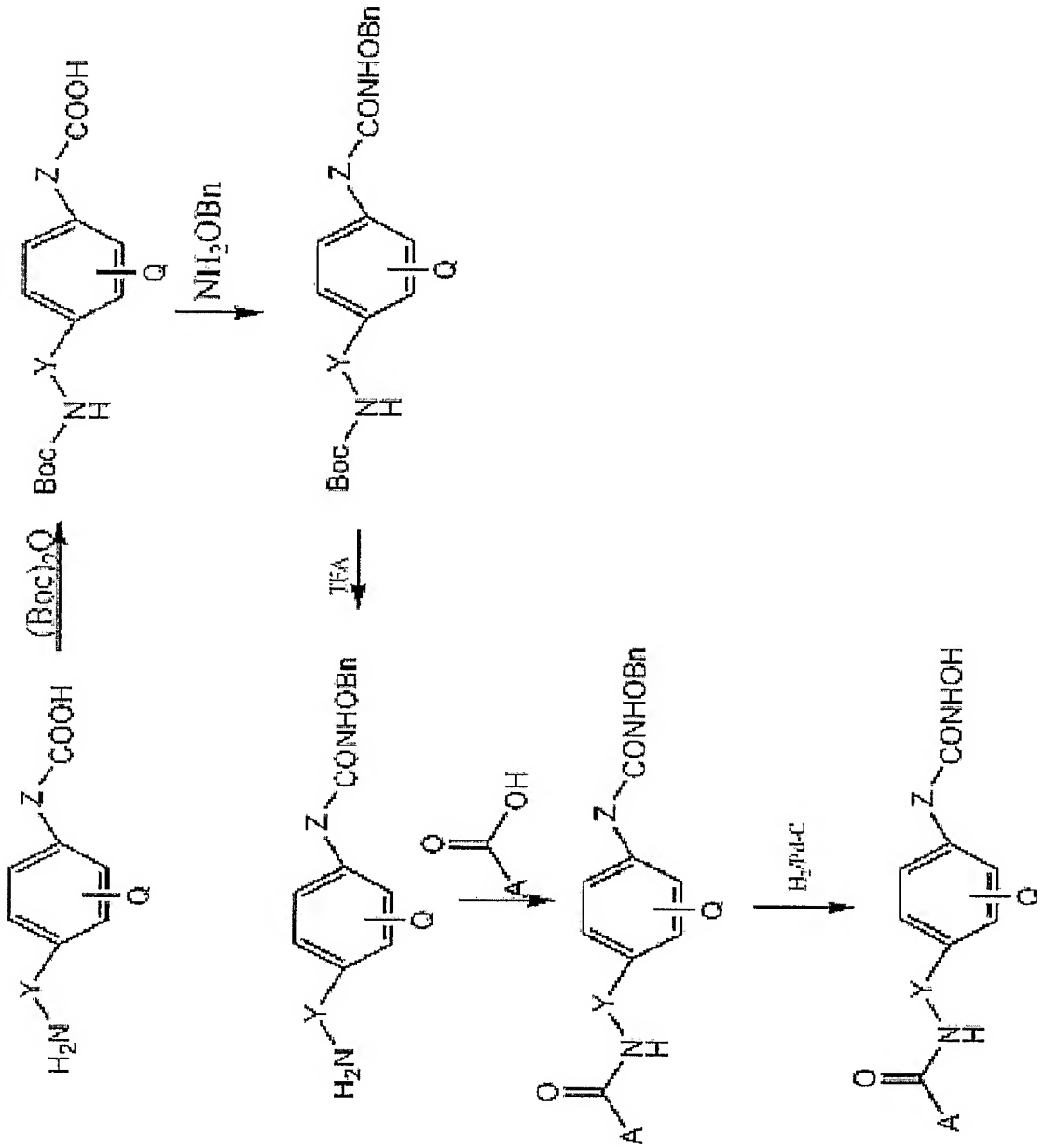


FIGURE 21